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F. Lindsey Scott
Suite B
2329 Coit Road
Plano, TX 75075

EXAMINER	
HILL, KEVIN KAI	
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1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/769,034	KONDURI ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-19,22-30,33-39,42-50,52 and 53* is/are pending in the application.

4a) Of the above claim(s) *6,14,15,30,31,46,47 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-13, 16-19, 22-29, 32-38, 41-45, 48-49 and 52* is/are rejected.

7)☒ Claim(s) *4,13 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

Applicant's amendments to Claims 1-5, 8-10, 12-13, 18-19, 22-23, 25-26, 29-30, 35-37, 39, 46, and 49-50, in the reply filed December 11, 2006, is acknowledged. Claims 7, 20-21, 31-32, 40-41 and 51 have been cancelled without prejudice. Claims 6, 14-15, 28, 31-32, 47-48 and 52 have been withdrawn without prejudice. Also acknowledged is Applicant's new Claim 53, which have been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group. Some claims have been renumbered by the Examiner (see Claim Objection below) in this office action.

It is noted that in the amendment filed December 11, 2006, Applicant states on page 2, Amendments to the Claims, lines 5-7, that Claims 14-15 have been both cancelled and withdrawn. Both conditions cannot simultaneously exist. The instant claim set indicates the status of Claims 14-15 to be withdrawn, and unless otherwise indicated, the Examiner will consider the claims as not cancelled.

Claims 6, 14-15, 30-31, 46-47 and 51 are pending, but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-5, 8-13, 16-19, 22-29, 32-38, 41-45, 48-49 and 52 are under consideration.

Priority

The Applicant's claim for priority under 35 U.S.C. 120 regarding the U.S. Provisional Application 60/498,609, filed on August 28, 2003 and U.S. Provisional Application 60/498,546, filed on August 28, 2003 is acknowledged.

Specification

1. **The disclosure is objected to because of the following informalities**: The specification is inconsistent regarding the use of hyphenated terms. For example, the specification discloses sterically stabilized liposomes as:

ai) phosphatidylcholine, phosphatidylglycerol, and poly(ethylene glycol)-distearyolphosphatidyldiethanolamine [0033] and [0050],

aii) phosphotidylglycerol-phosphotidylcholine-poly(ethylene glycol)-distearoylphosphatidylethanolamine-cholesterol [0051], and

aiii) phosphatidylcholine, phosphatidylglycerol-poly(ethylene glycol) distearoylphosphatidylethanolamine-cholesterol [0081], and

bi) chloroform-methanol-2:1 [0051], and

bii) chloroform:methanol, 2:1 [0081].

Are these the same structures or different structures?

One of ordinary skill in the art would reasonably interpret the use of the hyphen to indicate a covalent bond between the two compounds, and the use of the comma or colon to indicate the absence of a covalent bond between the disclosed compounds. For example, it is commonly understood in the art that chloroform is not covalently bonded to methanol. Furthermore, the specification discloses Applicant's contemplation of poly(ethylene glycol) conjugated to lipids [0029-0030], wherein the term 'poly(ethylene glycol)-lipid' is used to indicate the covalent conjugation.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999).

The ambiguous use of hyphenated terms in the instant specification does not clearly define the inventive subject matter.

It is suggested that the specification be amended to use hyphenated compounds only when said compounds are covalently bonded together, e.g. poly(ethylene glycol)-distearyolphosphatidyldiethanolamine [0050], and that the compositions comprising compounds that are not covalently bound together be indicated using commas or colons, e.g. 'phosphatidylcholine, phosphatidylglycerol, and poly(ethylene glycol)-distearyolphosphatidyldiethanolamine' [0033] and 'chloroform:methanol, 2:1' [0081].

If Applicant in fact contemplates the sterically stabilized liposome to comprise components that are covalently bound together, e.g. phosphotidylglycerol-phosphotidylcholine-poly(ethylene glycol)-distearoylphosphatidylethanolamine-cholesterol, as well as sterically stabilized liposome comprising components that are not non-covalently bound together, e.g. phosphatidylcholine, phosphatidylglycerol, poly(ethylene glycol) and cholesterol, then a statement declaring such contemplation is required in addition to the use of precise terminology so as to clearly apprise the Examiner and the artisan which liposome compositions comprise covalently bonded components from those liposome compositions comprising non-covalently bonded components.

Appropriate correction is required.

Claim Objections

2. **The prior objection to Claim 28 is maintained** because the original claim was absent, and Applicant has merely withdrawn, rather than cancelled, the claim.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Because Claim 28 never existed in the claim set, all claims subsequent to Claim 28 have been renumbered. This revised numbering of the claims is heretofore applied in the instant office

action. Accordingly, misnumbered claims 29-39, 42-50 and 52-53 have been renumbered 28-38, 41-49 and 51-52.

3. **The prior objection to Claim 29 is withdrawn** because Applicant has amended the claim to address the relevant issue(s).

4. **Claims 4, 13 and 45 are newly objected to because of the following informalities**:

With respect to Claim 4, Applicant is advised that should Claim 3 be found allowable, Claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

With respect to Claim 13, it appears that a conjunction is absent. See, for example, Claim 45.

With respect to Claim 45, the term 'contains' in the amended claim is not underlined so as to clearly indicate changes in recitation. See, for example, Claim 13.

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. **Claims 1, 9-10, 12-13, 16-18, 34, 37-38, 41-42, 44-45 and 48-49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims 1, 3-4, 12, 16-18, 35, 38-39, 42-43, 45-46, 49-50, 53 and 55-56 of copending Application No. 11/442,907. Although the conflicting claims are not identical, they are not patentably distinct from each other because the sterically stabilized liposome carrier composition and method of using said composition is reasonably embraced by the claims of the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claims 34-38, 41-45 and 48-49 stand rejected under 35 U.S.C. 112, first paragraph,** because the specification, while being enabling for a method for treating a respiratory tract of a mammal by aerosol administration of an effective amount of a composition comprising a sterically stabilized liposome carrier for combination with a drug, and a drug, the sterically stabilized liposome carrier consisting of phosphatidylglycerol (PG), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) and cholesterol (Chol) (PG:PC:PEG-DSPE:Chol) that is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone, does not reasonably provide enablement for all possible formulations and sterically stabilized liposomes component combinations that are compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

These claims are broad for encompassing a method of treating a respiratory tract of a mammal by aerosol administration of a large genus of liposome formulations of diverse component compositions. The inventive concept in the instant application is a sterically stabilized liposome whose structural properties yield the physiological property of being compatible with a mammalian respiratory tract, and via aerosol administration yield the pharmacological property of extending the effective life of the drug delivered in the respiratory tract by a time equal to at least twice the effective life of the drug alone in the respiratory tract.

These broad aspects are aspects that, given the nature of the invention, state of the prior art, and Applicant's disclosure, the Artisan would have to perform such experimentation as to essentially invent Applicant's subject matter.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The art has long recognized the existence of sterically stabilized liposome compositions, e.g. the formulation consisting of dicetylphosphate (DCP), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE), and cholesterol (Chol) (DCP:PC:PEG-DSPE:Chol) (Deol et al, Biochimica et Biophysica Acta 1334: 161-172, 1997a), wherein the phospholipids used in liposome formulation, such as phosphatidylcholine and phosphatidylglycerol, may be derived from egg yolk or soybeans (Waldrep et al, U.S. Patent No. 5,958,378, column 5, lines 32-35, September 28, 1999). Similarly, Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001) teach a method to make sterically stabilized liposomes, also known as "PEG-liposomes", that are an improved drug delivery system of polymer-coated liposomes, wherein the polymer, such as PEG, is covalently conjugated to one of the phospholipids and provides a hydrophilic cloud outside the vesicle bilayer... allowing the sterically stabilized liposome to... increase the pharmacological efficacy of encapsulated agents (column 3, lines 20-45). One factor demonstrated to affect the circulation half-life of the sterically stabilized liposome is that the PEG should have a molecular weight of approximately 2,000 Da, which is within the 500 to 5,000 Da range recited in Claim 8 of the instant application. According to Onyuksel et al, liposomes may be produced from combinations of lipid materials

well-known and routinely used in the art to produce liposomes and including at least one lipid component covalently bonded to a water-soluble polymer (columns 7-8, joining paragraph). Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains. Onyuksel et al teaches that polymers may include any compounds known and routinely used in the art of sterically stabilized liposome technology..., for example... PEG, preferred lipids such as PEG-DSPE, PC, and phosphatidylglycerol (PG), wherein the PC and PG may be egg-derived (column 14, lines 17-18) as recited in Claims 16 and 17 of the instant application, in further combination with cholesterol (Chol). It is noteworthy that one sterically stabilized liposome embodiment disclosed by Onyuksel et al is a liposome comprising the embodiment disclosed in the instant application, PG:PC:PEG-DSPE:Chol (column 8, lines 4-8; Example 2, column 14, lines 16-20), wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da, as disclosed by the composition limitations of the instant application. Thus, the level of one of ordinary skill in the art to manufacture sterically stabilized, or "stealth", liposomes is relatively high.

However, the art does not provide general guidance to demonstrate that sterically stabilized liposomes, such as the PG:PC:PEG-DSPE:Chol embodiment disclosed in the instant application and also taught by Onyuksel et al, can extend the life of a drug by two- to three-fold, as compared to free drug alone, in the respiratory tract of a mammal via aerosol delivery. The art teaches that stealth liposomes may be stable in the lungs for up to 4 days (the duration of the experiment), slow and control release of their encapsulated contents, e.g. isoniazid or rifampicin, and decrease the toxicity of the drug, compared to a non-encapsulated drug (Deol et al, Figures 3, 5 and 6, and Table 2). In particular, the cited references administered the stabilized liposomes by intravenous injection (in addition to Deol et al, 1997a and Onyuksel et al, 2001 above, see also Deol et al, June, Antimicrobial Agents and Chemotherapy 41(6): 1211-1214, 1997b and Zhang et al, Pharmaceutical Research 15(3): 455-460, 1998), and not by nebulization as taught in the instant specification. Furthermore, assays such as blood pressure (Zhang et al) or microbial colony-forming units in the lung, liver or spleen (Deol et al, 1997b) were used to evaluate drug efficacy, as compared between free drug and stealth liposome delivery, and have not shown an at least two-fold extension of the effective life of the drug. Thus, at the time of the invention,

considerable unpredictability in the art existed regarding the ability of a sterically stabilized liposome, even the PG:PC:PEG-DSPE:Chol embodiment disclosed in the instant application and also taught by Onyuksel et al, to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug.

The Amount of Direction Provided by the Inventor and The Existence of Working Examples

The specification teaches that the inventive liposomes are "tailored to be compatible with naturally-occurring fluids found in the lung" so that the sterically stabilized liposomes provide long stability in the lungs (page 7, lines 20-25). However, the specification discloses a broad genus of compounds with which an artisan may use to create a liposome, many of which were already known in the art at the time of the invention, in particular the PG:PC:PEG-DSPE:Chol liposome component combination of the instant application (Onyuksel et al, column 8, lines 4-8; Example 2, column 14, lines 16-20). Furthermore, the specification does not teach several important considerations, such as the quantified, necessary amounts of each liposome component and their respective molar ratios such that the final liposome product will: a) be compatible with naturally-occurring fluids found in the lung so that the sterically stabilized liposomes provide long stability in the lungs, and importantly, b) extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug (pages 7-8, joining paragraph). Rather, the only example of a sterically stabilized liposome provided in the specification to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug is a sterically stabilized liposome whose structural composition was previously disclosed by Onyuksel et al consisting of PG:PC:PEG-DSPE:Chol. Yet, the respective molar ratios of each component of the exemplified PG:PC:PEG-DSPE:Chol liposome in the instant specification so as to distinguish it from the prior art and make manifest the property of extending the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug are not disclosed in the instant application.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create

an undue burden for a person of ordinary skill in the art to demonstrate that a liposome consisting of any one of all possible combinations of liposome components disclosed in the instant specification will yield a sterically stabilized liposome to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed product and method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method for treating a respiratory tract of a mammal by aerosol administration of an effective amount of a composition comprising a sterically stabilized liposome carrier for combination with a drug, and a drug, the sterically stabilized liposome carrier consisting of phosphatidylglycerol (PG), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) and cholesterol (Chol) (PG:PC:PEG-DSPE:Chol) that is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone, is proper.

Applicant's Arguments

Applicant's argue that the enablement rejection is inappropriate given the limiting recitation of the carrier to contain a single drug, budesonide, and that it is "hard to believe that anyone skilled in the art could not review Applicant's specification and prepare the materials necessary and administer the materials as disclosed".

Applicant's' arguments have been fully considered but are not found persuasive. It appears that Applicant has missed the point the Examiner was trying to make, specifically the inability to reasonably extrapolate to the larger genus of liposome formulations of diverse component compositions encompassed by the claims based upon a single liposome example. The drug carried by the liposome is immaterial to the enablement rejection.

The specification teaches that the inventive liposomes are "*tailored* [emphasis added] to be compatible with naturally-occurring fluids found in the lung" so that the sterically stabilized liposomes provide long stability in the lungs (page 7, lines 20-25), but does not teach several important considerations, such as the quantified, necessary amounts of each liposome component

and their respective molar ratios such that the final liposome product will: a) be compatible with naturally-occurring fluids found in the lung so that the sterically stabilized liposomes provide long stability in the lungs, and importantly, b) extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug (pages 7-8, joining paragraph), if not three times the effective life (Claim 2 and 19). The only example of a sterically stabilized liposome to extend the effective life of a drug in a mammalian respiratory tract by a time at least equal to twice that of free drug provided in the specification is a sterically stabilized liposome consisting of PG:PC:PEG-DSPE:Chol. Importantly, the respective molar ratios of each component of this single liposome example are not disclosed and the prior art does not provide the necessary teachings to make up for this deficiency. One of ordinary skill in the art cannot reasonably extrapolate the inadequate disclosure of this single liposome formulation species to an entire genus of liposome formulations, and reasonably expect that all possible formulation species embraced by the genus will perform according to the inventive method.

7. **Claims 3-5, 9-11, 22, 27, 35, 37-38, 42-43 and 52 are rejected under 35 U.S.C. 112 first paragraph**, because the specification as originally filed does not describe the invention as now claimed. The newly recited claims contain element(s) that are now considered to be new matter.

With respect to Claims 3-5, 22, 35 and 37-38, the Examiner is unable to find support in the instant specification or the parent provisional applications 60/498,546 or 60/498,609 for the instant recitations regarding the specific amounts of phosphatidylglycerol and phosphatidylcholine to be present in the sterically stabilized liposome. The instant specification [0026] clearly states that the sterically stabilized liposome comprises phosphatidylcholine. Paragraph [0027] then states: "Alternatively, the sterically stabilized liposomes may also include significant quantities, up to 50%, of head groups comprising phosphatidylglycerol. This mixed material is considered to be somewhat more compatible with lung fluids than is phosphatidylcholine alone." This statement, however, does not clearly define the invention as to whether the liposome contains up to 50 wt.% phosphatidylglycerol as measured according to the all of the liposome carrier components, or up to 50 wt.% phosphatidylglycerol, as measured

according to the amount of phosphatidylcholine present in the liposome. Furthermore, Claims 3-4 recite the composition to comprise up to 99% phosphatidylglycerol of the phosphatidylcholine and phosphatidylglycerol phospholipid content. The Examiner is unable to find support for the instantly recited values.

With respect to Claim 9, the original disclosure fails to specify the poly(ethylene glycol) attached to cholesterol as now claimed. The specification discloses that "Any of the head groups or the poly(ethylene glycol), may be attached to acyl groups containing from about 8 to about 18 carbon atoms. Preferably, from about 8 to about 18 carbon atoms are present in the acyl groups. Such groups comprise distearoyl, stearoyl oleoyl, stearoyl palmitoyl, dipalmitoyl, dioleoyl, palmitoyl oleoyl and dipalmitoleoyl" [0029]. The specification does not disclose the instantly recited poly(ethylene glycol) attached to cholesterol. Furthermore, the art recognizes that cholesterol contains 27 carbon atoms, and thus is outside the instant disclosure of lipids containing 8 to 18 carbon atoms.

With respect to Claims 10 and 42, the specification is silent regarding the contemplation of explicitly excluding acyl chains having less than 16 carbon atoms.

With respect to Claims 11, 27 and 43, the specification is silent regarding the explicit contemplation of poly(ethylene glycol) attached to oleoyl stearoyl acyl groups. As noted above, the contemplation of stearoyl oleoyl [0029] is supported. Unless otherwise indicated on the record, it is the Examiner's position that the recitation of 'oleoyl stearoyl' is structurally distinct from 'stearoyl oleoyl'.

With respect to Claim 52, the Examiner interprets the term 'distearoylphosphatidylethanolamine-cholesterol' to mean that distearoylphosphatidylethanolamine and cholesterol are covalently bonded. There is no support in the specification for a covalent bonding between these to compositions. See also the discussion above (1. Specification).

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN

INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*" (emphasis added).

For reasons set forth above, the amendment filed December 11, 2006 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, Applicant is invited to specifically point out where in the specification the support can be found for the amendment made to the disclosure.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **The prior rejection of Claims 8 and 25 under 35 U.S.C. 112, second paragraph is withdrawn** because Applicant has either cancelled or amended the claim to address the relevant issue(s).

9. **Claims 3-5, 23-26, 35 and 52 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to Claims 3-5, the claims recite the relative ratio of phosphatidylcholine and phosphatidylglycerol. However, the liposome carrier comprises at least three elements, and the claims do not recite the total phospholipid content of the carrier so as to render the relative ratios of two phospholipids indefinite. See Claims 22-23, for example.

With respect to Claims 23-25, the claims are dependent on claims that have been cancelled (Claims 20-21).

With respect to Claim 26, the claim recites the limitation "poly(ethylene glycol)-derivatized lipid" in reference to Claim 18. There is insufficient antecedent basis for this limitation in the claim. This is a new ground of rejection.

With respect to Claim 35, the claim is drawn to the liposome carrier comprising phosphatidylcholine. The additional recitation of "wherein at least 50 percent of the head groups contain phosphatidylcholine" is indefinite. If only 50% of the phosphatidylcholine head groups do not contain phosphatidylcholine, then by definition those compounds are not phosphatidylcholine. If instead, the further limitation refers to Claim 35, then the claim lacks antecedent basis, as the term 'head groups' is not recited in Claim 35 so as to identify which head groups of which compound should not have phosphatidylcholine. See, for example, the recitation of Claim 5.

With respect to Claim 52, where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "distearoylphosphatidylethanolamine-cholesterol" in Claim 53 is used by the claim to mean "distearoylphosphatidylethanolamine is covalently bonded to cholesterol", while the accepted meaning is "distearoylphosphatidylethanolamine and cholesterol, wherein the two compounds are <u>not</u> covalently bonded to each other". The term is indefinite because the specification [0050] does not clearly redefine the term. See also the discussion above (1. Specification; 6. New Matter).

Appropriate correction or clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. **The prior rejection of Claims 18-27, 28-30, 32-33 under 35 U.S.C. 102(b) is withdrawn.** Applicant has either cancelled or amended the claims to address the relevant issue(s).

11. **The prior rejection of Claims 1, 5, 8-13 and 16-17 stand and added Claim 52 is newly rejected under 35 U.S.C. 102(b),** as being anticipated by Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001).

The claims are drawn to a composition comprising a sterically stabilized liposome carrier for combination with a drug.

Onyuksel et al teach a method to make sterically stabilized liposomes, also known as "PEG-liposomes" and "stealth liposomes" that are an improved drug delivery system of polymer-coated liposomes, wherein the polymer, such as PEG, is covalently conjugated to one of the phospholipids and provides a hydrophilic cloud outside the vesicle bilayer... allowing the sterically stabilized liposome to... increase the pharmacological efficacy of encapsulated agents (column 3, lines 20-45). According to Onyuksel et al, liposomes may be produced from combinations of lipid materials well-known and routinely used in the art to produce liposomes and including at least one lipid component covalently bonded to a water-soluble polymer (columns 7-8, joining paragraph). Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains.

With respect to the limitations of Claim 1, Onyuksel et al teaches that the liposomes produced according to the methods of the invention are characterized by improved stability and biological activity and are useful in a variety of therapeutic... applications, such as asthma, and

may be delivered by aerosol administration, nebulization, inhalation, insufflation, or intratracheally (column 8, lines 7-10, 31 and 44-49).

With respect to the limitations of Claims 5, 8-12, 16-17 and 53, Onyuksel et al also discloses that polymers may include any compounds known and routinely used in the art of sterically stabilized liposome technology..., for example... phosphatidylcholine (PC), and phosphatidylglycerol (PG), wherein the PC and PG may be egg-derived (col. 3, lines 25-29; col. 14, lines 17-18), poly(ethylene glycol) (PEG), wherein PEG is covalently conjugated to phospholipids, e.g. distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE; col. 8, line 1), in further combination with Chol. For example, Onyuksel et al discloses a liposome structural composition embodiment also disclosed in the instant application, that is PG:PC:PEG-DSPE:Chol (col. 8, lines 1-8; Example 2, col. 14, lines 16-20), wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da. With respect to the limitations of Claims 7-8, 24-27 and 29 Onyuksel et al discloses that one factor demonstrated to affect the circulation half-life of the sterically stabilized liposome is that the PEG should have a molecular weight of approximately 2,000 Da, which is within the 500 to 5,000 Da range recited in Claim 8 of the instant application. Claim 53 is included to the extent that it is interpreted as the liposome carrier contains DSPE and cholesterol, not DSPE covalently bonded to cholesterol.

With respect to the limitations of Claims 2 and 13, Onyuksel et al discloses a liposome structural composition embodiment also disclosed in the instant application, that is PG:PC:PEG-DSPE:Chol (column 8, lines 4-8; Example 2, column 14, lines 16-20), wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da, as disclosed by the composition limitations of the instant application. Onyuksel et al also do not disclose that the inventive liposome formulations within the scope of the invention effectively extends the life of the drug by at least two or three times the drug alone. However, given that Onyuksel et al disclose an embodiment disclosed in the instant application, absent evidence to the contrary, said PG:PC:PEG-DSPE:Chol liposome would inherently possess the ability to extend the effective life of the drug, as compared to drug alone, because the liposome component formulation of Onyuksel et al is indistinguishable from the instant application.

Thus, Claims 1, 5, 8-13 and 16-17 are anticipated by Onyuksel et al.

Applicant's Arguments

Applicant's argue that the reference of Onyuksel et al is not considered appropriate because Onyuksel et al do not teach the drug to be budesonide, the instantly elected drug embodiment.

Applicant's' argument has been fully considered but is not found persuasive. The reference of Onyuskel et al was/is applied to the claims reciting the liposome carrier, and a liposome carrier further comprising a drug. The drug is not germane to claims drawn to the liposome carrier composition. Although the preamble of Claim 1 recites "for combination with budesonide", there is nothing in the specification disclosing a factor or formulation that is specific and critical for the inventive liposome carrier to contain budesonide, while also rendering the carrier incapable of carrying any other drug. Rather, it is the Examiner's position that the sterically stabilized liposome carrier, as recited in the claims and disclosed in the specification, may carry a genus of structurally distinct drugs. As recited, Onyuksel et al fully anticipates the formulations of the instantly recited liposome carrier. It is also noted that Applicant's acknowledge (pg 10, last ¶) that the method of making sterically stabilized liposomes and materials for doing so were well known to those skilled in the art many years before the Onyuksel reference.

The reference of Onyuksel et al was not applied to claims directed to Applicant's composition comprising a sterically stabilized liposome and the drug budesonide. Applicant's have amended Claims 18-19, 22-23, 25-26, 29-30, and thus Onyuksel et al no longer anticipates the composition recited in Claims 18-19, 22-23, 25-26, 29-30.

Applicant's note that the liposomes discussed by Onyuksel et al apparently have a diameter of less than about 300 nanometers, which is considerably larger than Applicant's preferred sizes, and thus Onyuksel et al is not relevant art.

Applicant's' argument has been fully considered but is not found persuasive. The Examiner notes that such size limitations of the sterically stabilized liposome are not recited in the claims, and therefore were/are not found to be germane during examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. **The prior rejection of Claims 1, 5, 14-15, 18, 30-31 and 34-50 under 35 U.S.C. 103(a) is withdrawn.** Applicant's argument regarding the references of Konduri et al (J. Allergy Clin Immunology, Supplement, 107(2): S315, 2001) and Waldrep (Abstract only, Drugs Today 34(6): 549-561, 1998) are found to be persuasive.

13. **Claims 1-2, 5, 8-13, 16-17 and 52 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001) in view of Waldrep et al (U.S. Patent No. 5,958,378; September 28, 1999) and, as evidenced by Konduri et

al (J. Allergy and Clinical Immunology: 111(2): 321-327, 2003; available online April 9, 2003; * of record).

The claims are drawn to a sterically stabilized liposome carrier containing phosphatidylcholine (PC), phosphatidylglycerol (PG) and poly(ethylene glycol) (PEG) for combination with a drug, wherein said liposome carrier is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone.

Onyuksel et al teach that polymers known and routinely used in the art of sterically stabilized liposome technology..., include for example... PC, PG, wherein the PC and PG may be egg-derived (col. 3, lines 25-29; col. 14, lines 17-18), PEG, wherein PEG may be covalently conjugated to phospholipids, e.g. distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE; col. 8, line 1), in further combination with cholesterol (Chol). For example, Onyuksel et al discloses a liposome embodiment also disclosed in the instant application, that is PG:PC:PEG-DSPE:Chol (col. 8, lines 1-8; Example 2, col. 14, lines 16-20), wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da. Onyuksel et al discloses that one factor demonstrated to affect the circulation half-life of the sterically stabilized liposome is that the PEG should have a molecular weight of approximately 2,000 Da, which is within the 500 to 5,000 Da range recited in the instant application. Claim 52 is included to the extent that it is interpreted as the liposome carrier contains DSPE and cholesterol, not DSPE covalently bonded to cholesterol. Onyuksel et al teach that the liposomes produced according to the methods of the invention are characterized by improved stability and biological activity and are useful in a variety of therapeutic... applications, such as asthma, and may be delivered by aerosol administration, nebulization, inhalation, insufflation, or intratracheally (column 8, lines 7-10, 31 and 44-49).

Onyuksel et al do not disclose that the inventive liposome formulations within the scope of the invention effectively extends the life of the drug by at least two or three times the drug alone. However, Onyuksel et al disclose a PG:PC:PEG-DSPE:Chol liposome embodiment reasonably embraced by the generic PG:PC:PEG-DSPE:Chol liposome formulation as taught by Konduri et al to extend the effective life of the drug, as compared to drug alone, and thus absent

evidence to the contrary, said PG:PC:PEG-DSPE:Chol liposome of Onyuksel et al would inherently possess the instantly recited ability because the liposome formulation of Onyuksel et al is indistinguishable from Konduri et al.

Onyuksel et al do not explicitly teach the phospholipids to contain stearoyl oleoyl, stearoyl palmitoyl, dipalmitoyl, dioleoyl, palmitoyl oleoyl and dipalmitoleoyl. However, Onyuksel et al teach that liposomes may be produced from combinations of lipid materials well-known and routinely used in the art to produce liposomes and including at least one lipid component covalently bonded to a water-soluble polymer (columns 7-8, joining paragraph). Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains. Furthermore, at the time of the invention, Waldrep et al taught the formulation of liposome carrying the drug budesonide, wherein other phospholipids might be substituted for DLPC, representative examples of suitable phospholipids including egg yolk phosphatidylcholide, hydrogenated soybean phosphatidylcholide, dimyristoyphosphatidylcholide, diolyeolyl-dipalmitoyleolylphosphatidylcholide and dipalmitoyl phosphatidylcholide (col. 5, lines 30-36). Thus, it would be reasonable to conclude that one of ordinary skill in the art would contemplate the use of the instantly recited acyl groups for use in liposome carriers, as they are lipid materials well known and routinely used in the art.

Onyuksel et al do not explicitly teach the liposome carrier to contain phosphatidylinositol, dipalmitoylphosphatidylpolyglycerol, lipid conjugated polyoxyethylene, lipid conjugated polysorbate, or lipids conjugated to other hydrophilic steric coating molecules safe for *in vivo* use. However, Onyuksel et al references the prior art teaching the use of other lipids for use in liposomes, e.g. polyoxyethylene-lipid conjugates (Trubetskoy et al).

It would have been obvious to one of ordinary skill in the art to modify the sterically stabilized liposome of Onyuksel et al to comprise other phospholipids with a reasonable chance of success because the art has long known of common phospholipids present in eukaryotic cell membranes, as taught by Waldrep et al. Furthermore, Applicant's acknowledge in the paper filed December 11, 2006 (pg 10, last ¶) that the method of making sterically stabilized liposomes and materials for doing so were well known to those skilled in the art many years before the Onyuksel reference. An artisan would be motivated to make such modifications because Onyuksel et al teach that "numerous modifications and variations in the invention... are *expected*

to occur (*emphasis added*) to those skilled in the art" (column 20, lines 54-57) and so as to optimize the delivery of the drug carried by the liposome to a desired target cell.

Thus, Claims 1-2, 5, 8-13, 16-17 and 52 are *prima facie* obvious.

14. **Claims 18-19, 22-27, 28-29, 32-38, 41-45 and 48-49 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Konduri et al (J. Allergy and Clinical Immunology: 111(2): 321-327, 2003; available online April 9, 2003; * of record) in view of Onyuksel et al (U.S. Patent No. 6,197,333 B1, March 6, 2001) and Waldrep et al (U.S. Patent No. 5,958,378; September 28, 1999).

The claims are drawn to a sterically stabilized liposome carrier in combination with the drug budesonide, and a method for treating a respiratory tract of a mammal by aerosol administration of an effective amount of a composition comprising a sterically stabilized liposome carrier for combination with a drug, and the elected drug being budesonide, the sterically stabilized liposome carrier consisting of phosphatidylglycerol (PG), phosphatidylcholine (PC), poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE) and cholesterol (Chol) (PG:PC:PEG-DSPE:Chol) that is compatible with the respiratory tract of a mammal and effective to extend the effective life of the drug in the respiratory tract by a time equal to at least twice the effective life of the drug alone, as enabled by the instant specification.

Konduri et al teach a sterically-stabilized liposome in combination with the drug budesonide for the treatment of mice in an experimental asthma model, and a method of treating a mammalian respiratory tract with said sterically-stabilized liposome carrier and budesonide (pg 322, Methods-Treatment Groups, Drugs and Reagents, Liposome Preparation). The sterically stabilized liposome contains phosphatidylglycerol, phosphatidylcholine, poly(ethylene glycol)-distearoylphosphatidylethanolamine (PEG-DSPE), and cholesterol, wherein the method of liposome formulation as taught by Gangadharam et al (reference cited therein) teaches that the phosphatidylcholine and phosphatidylglycerol are egg-derived, and the poly(ethylene glycol) has a molecular weight of 1,900 Da. Konduri et al teach that the sterically stabilized liposome containing budesonide was at least three times more effective than budenoside alone (Figures 1-5).

Konduri et al do not teach the specific formulation of the individual liposome carrier components, e.g., the phospholipid present in the liposome carrier to be at least 50% for phosphatidylcholine or up to 50% of phosphatidylglycerol.

However, at the time of the invention, Onyuksel et al taught the formulation of a sterically stabilized PG:PC:PEG-DSPE:Chol liposome (column 8, lines 4-8; Example 2, column 14, lines 16-20) in combination with a drug, wherein the PC was present in an amount of 50%, the PG was present in the amount of 10%, and the PEG had a molecular weight of 2,000 Da. Onyuksel et al disclose that one factor demonstrated to affect the circulation half-life of the sterically stabilized liposome is that the PEG should have a molecular weight of approximately 2,000 Da, which is within the 500 to 5,000 Da range recited in the instant application.

Neither Konduri et al nor Onyuksel et al explicitly teach the phospholipids to contain stearoyl oleoyl, stearoyl palmitoyl, dipalmitoyl, dioleoyl, palmitoyl oleoyl and dipalmitoleoyl. However, Onyuksel et al teach that liposomes may be produced from combinations of lipid materials well-known and routinely used in the art to produce liposomes and including at least one lipid component covalently bonded to a water-soluble polymer (columns 7-8, joining paragraph). Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains. Furthermore, at the time of the invention, Waldrep et al taught the formulation of liposome carrying the drug budesonide, wherein other phospholipids might be substituted for DLPC, representative examples of suitable phospholipids including egg yolk phosphatidylcholide, hydrogenated soybean phosphatidylcholide, dimyristoyphosphatidylcholide, diolyeolyl-dipalmitoyleolylphosphatidylcholide and dipalmitoyl phosphatidylcholide (col. 5, lines 30-36). Thus, it would be reasonable to conclude that one of ordinary skill in the art would contemplate the use of the instantly recited acyl groups for use in liposome carriers, as they are lipid materials well known and routinely used in the art.

It would have been obvious to one of ordinary skill in the art to modify the the sterically stabilized liposome of Konduri et al with the formulation as taught by Onyuksel et al with a reasonable chance of success because Onyuksel et al teach the successful production of a sterically stabilized liposome containing phosphatidylcholine and phosphatidylglycerol for therapeutic applications involving a mammalian respiratory tract. Onyuksel et al teach that the liposomes produced according to the methods of the invention are characterized by improved

stability and biological activity and are useful in a variety of therapeutic... applications, such as asthma, and may be delivered by aerosol administration, nebulization, inhalation, insufflation, or intratracheally (column 8, lines 7-10, 31 and 44-49). An artisan would be motivated to make such a modification because Konduri et al do not explicitly teach the exact formulation of their liposome carrier; whereas, Onyuksel et al provide quantitative values of the individual carrier components and their respective molar ratios, and thus provide the artisan with a solid position from which the artisan may synthesize sterically stabilized liposome carrier(s) for treating a respiratory tract of a mammal by aerosol administration.

It also would have been obvious to one of ordinary skill in the art to modify the sterically stabilized liposome of Konduri et al and Onyuksel et al to comprise other phospholipids with a reasonable chance of success because the art has long known of common phospholipids present in eukaryotic cell membranes, as taught by Waldrep et al. Furthermore, Applicant's acknowledge in the paper filed December 11, 2006 (pg 10, last ¶) that the method of making sterically stabilized liposomes and materials for doing so were well known to those skilled in the art many years before the Onyuksel reference. An artisan would be motivated to make such modifications because Onyuksel et al teach that "numerous modifications and variations in the invention... are *expected to occur* (*emphasis added*) to those skilled in the art" (column 20, lines 54-57) and so as to optimize the delivery of the drug carried by the liposome to a desired target cell.

Thus, Claims 18-19, 22-27, 28-29, 32-38, 41-45 and 48-49 are *prima facie* obvious.

Conclusion

15. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Q. JANICE LI, M.D.
PRIMARY EXAMINER